DEPARTMENT OF HEALTH AND HUMAN SERVICES **Public Health Service**

MEMORANDUM

DATE February 8,1999

FROM: Stephanie L. Simek, Ph.D.
Regulatory Coordinator, DARP.

TO: Dr. David Finbloom
Director
Division of Cytokine Biology

TO: The File

SUBJECT: Addendum to the Review of Container Closure, Drug Substance and Product Stability Data for INF-beta 1a**.**

TITLE: Original BLA Submission for Rebif (Interferon beta-1a) Injection

SPONSOR: Serono Laboratories Inc.
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Product: Interferon beta-1A

Addendum to Stability Review Document

This is an addendum to the stability review document, that addresses the responses submitted to the discipline review letter sent on January 29, 1999.
Serono was also requested to submit detailed protocols for conducting their stability studies and extending shelf-life of the REBIF® 22mcg and 44mcg pre-filled syringes.

Stability Protocol

Serono has submitted protocols for conducting stability studies of their REBIF® 22mcg and 44mcg pre-filled syringes. The shelf-life extensions will be based on real time data covering the proposed shelf-life and obtained on a minimum of XXXXXXXXXX batches. The guidances require that at least three batches of product be tested and that the data be based on full long-term stability data. With this commitment by Serono they may use these protocols

to develop data to support an extension of a retest or expiration dating period via annual reports under 21 CFR 314.70(d)(5). Serono commits to submitting further shelf-life data when it becomes available.

Shipping Validation

Serono has provided data from shipment validation studies that demonstrate that the bulk drug substance is maintained at XXXXXXXXXX. An SOP "Procedure for the packaging, inspection and shipment of Goods from XXXXXXXXXX" was submitted. Serono has adequately shown using a calibrated XXXXXXXXXX type temperature data logger, that the bulk substance is maintained at XXXXXXXXXX during shipment. Included is a protocol and supporting data to validate the XXXXXXXXXX weight required for maintaining the appropriate temperature under worse case external temperature conditions XXXXXXXXXX. Results from these studies demonstrate that IFN-beta-1a bulk substance can be maintained at or below XXXXXXXXXX for at least XXXXXXXXXX with the minimum weight of dry ice being set at XXXXXXXXX.

Also included in this document is an SOP to validate temperature control of IFN-beta-1a during shipment in different size bulk containers. These validation data provide evidence that IFN-beta-1a bulk solution, in XXXXXXXXXX as well as in XXXXXXXXXX and XXXXXXXXXX packed from the production sites to the final formulation sites, are maintained at or below XXXXXXXXXXX during shipment..

Serono was requested to submit data to validate shipment of the final formulated drug product to the distribution site. Serono has committed to provide under a separate cover data which validates the shipping conditions of the final formulated drug product to the distribution site in the United States. The company also commits to include SOPs describing test methods and how the data are recorded, when this data becomes available.

Stability Testing of Drug Substance

Serono provided real time stability data for the production batch XXXXXXXXXX for up to XXXXXXXXXX months. This data can be applied to the already existing XXXXXXXXXX data on two other production lots and provides XXXXXXXXXXX stability data for XXXXXXXXXX full production lots. This data confirms the stability of the drug substance when stored at XXXXXXXXXX and is consistent with the company's proposed XXXXXXXXXX retest period for drug substance.

As requested further real time stability data was also submitted for qualification lots, XXXXXXXXXX. The current real time stability data increases the dating period up to XXXXXXXXXX. This data demonstrates that the qualification batches are consistent with data submitted on the production batches.

The data from the additional production batch and the three qualification lots demonstrate that there is no significant change observed in the antiviral activity, protein content and XXXXXXXXXX content. There is a slow marginal increase in the level of XXXXXXXXXX products but this increase still remains within the specification limits.

Stability of Drug Product

Serono was requested to submit real time and accelerated stability data for 6 batches of REBIF® (3 of REBIF® 22mcg and 3 of REBIF® 44mcg) beyond the originally submitted XXXXXXXXXX test periods. Currently Serono has real time stability data for XXXXXXXXXX REBIF® 22mcg and XXXXXXXXXX REBIF® 44mcg batches at XXXXXXXXXX and XXXXXXXXXXX data for XXXXXXXXXX REBIF® 22mcg and XXXXXXXXXX REBIF® 44 mcg batches. All batches tested remained within specification, however, a slow trend to an increase of XXXXXXXXXX is observed for all batches.

Three batches of REBIF® 22mcg and three batches of REBIF® 44mcg in pre-filled syringes have been tested for up to XXXXXXXXXX. The trend toward XXXXXXXXXX is visible with a maximum of XXXXXXXXXX reached after XXXXXXXXXX in one batch. A slight trend to form XXXXXXXXXX is observed at XXXXXXXXXXX. In addition, a XXXXXXXXXX. While all batches are within the XXXXXXXXXX specification limit after XXXXXXXXX of storage at XXXXXXXXXX. The other test parameters remained unchanged over the XXXXXXXXXX test period.

The current data would support a shelf life claim of XXXXXXXXXX 2-8°C, with an extension being granted as stated in 21 CFR 314.70(d)(5) with submission of further supportive data.

Container/Closure

The responses submitted regarding the container closure will be reviewed by the CDRH consultant and will be addressed under another review memo.